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THEORETICAL JUSTIFICATION OF A PURPOSEFUL SEARCH OF POTENTIAL NEUROTROPIC DRUGS

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A targeted search for potential drugs of neurotropic action involves the choice of a basic “pharmacophore”, which is advisable to carry out on the basis of the achieved principle among the classes of chemical compounds where active pharmaceutical substances with high targeted activity have already been identified. Therefore, the pyrrolidine core, which is the basic fragment of nootropics of the racetam group, is promising for the rational design of biologically active compounds of nootropic action. Its combination with other heterocyclic fragments, in particular, the 1,2,4-triazole ring, allows for these “hybrid” molecules to expect a permanent change in the magnitude of the pharmacological effects. Creation of a virtual library of compounds, 3D-pharmacophore screening and molecular docking is a promising way to optimize a targeted search for substances with a given pharmacological activity.

The aim. To optimize targeted search for new nootropic compounds.

Materials and methods. The base generation for the virtual screening was carried out using the Marvin Sketch 20.5 software. For receptor-oriented flexible docking, the Autodock 4.2 software package was used.

Results. New derivatives of 1-benzyl-4-pyrrolidin-2-one were selected as the object of the study. Based on the results of the 3D pharmacophore screening and molecular docking to nootropic targets of the virtual base compounds, scoring functions were calculated. A detailed analysis of the geometrical arrangement of “hit compounds” at the active sites of nootropic receptors (PDB ID: 5UOW, 5CXV, 6PV7) made it possible to formulate hypotheses regarding possible ways of interaction of “hybrid” compounds with biotargets.

The activity of promising molecules with respect to the studied receptors can be realized by creating complexes between them, the stability of which is ensured mainly due to the energetically favourable geometric arrangement of ligands in the active center of these acceptors, the formation of hydrogen bonds between them, and intermolecular electrostatic and donor-acceptor interactions.

Conclusions. Structural modification of the pyrrolidine ring by combining with 1,2,4-triazole scaffold containing substituents of various electronic nature has been proposed. Using 3D-pharmacophore screening, the virtual base of 1-benzyl-4-pyrrolidin-2-one derivatives was analyzed in order to search among them for new molecules of nootropic action. Docking studies have identified a promising group of derivatives of 1-benzyl-4 (4-R-5-sulfanylidene-4,5 dihydro-1H-1,2,4-triazol-3-yl) pyrrolidin-2-one, which have affinity for nootropic biotargets and are promising for further synthetic and pharmacological studies

Keywords: 1-benzyl-4-pyrrolidin-2-one derivatives, virtual screening, nootropic action, molecular docking

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1. Introduction

The search for new chemical structures capable of exhibiting specific biological action is a complex problem that requires the use of modern methods of molecular modelling and it is advisable to carry out in the class of chemical compounds where substances with a specific directional action have already been identified. At the research planning stage, we analyzed the current range, chemical structure and mechanisms of action of existing drugs.

Currently, there are many drugs with nootropic action of different chemical structure, which act on the relevant biological targets and, as a consequence, have a

wide range of pharmacological activity [1, 2]. Ginkgo biloba drugs have neuroprotective effects and also act as antioxidants and antiapoptotics, inhibiting caspase-3 activation and amyloid aggregation in the direction of Alzheimer's disease. Acetylcholine esterase (AChE) inhibitors eliminate the symptoms of Alzheimer's disease. However, there is little systematic data on the effect of cholinergic treatment on cognitive function in normal individuals [3, 4]. Strategies to improve learning and memory are aimed at ways to increase the plasticity of the brain. Phosphodiesterase inhibitors such as rolipram and NMDA-modulating drugs such as donepezil and D-cycloserine, modafinil and methylphenidate are used to

enhance attention and alertness [5, 6]. Referring to the fact that most nootropic agents do not have clear mechanisms of action, there is a practical application of most of them in the treatment of brain injuries [7].

Studies of the modern domestic pharmaceutical market of nootropic drugs revealed that Ukraine registered 24 active substances from the list of international non-proprietary names of the World Health Organization, represented by 107 names [8, 9]. At the same time, domestic drugs prevail in quantitative terms (60.2 %), although the main profit from sales is provided by imported pharmacotherapeutic nootropic drugs (76 %). Cerebrolysin, piracetam and phenotropil are the leaders in the price rating of nootropic drugs [10].

At the first stage of synthesis planning, in order to theoretically substantiate the choice of the basic structure, we used the accumulated empirical experience, logical-structural analysis and "hybrid-pharmacophore approach". The basis of the chemical structure of one of the promising groups of psychoactive nootropic drugs of the group of racetams (piracetam, aniracetam, oxiracetam, pramiracetam, phenylpiracetam, levetiracetam, nefiracetam, nebracetam and coluracetam) is the pyrrolidine cycle [11, 12]. Piracetam, a derivative of the neurotransmitter γ -aminobutyric acid (GABA), has a variety of physiological effects that may be due in part to the restoration of cell membrane fluidity. At the neuronal level, piracetam modulates neurotransmission in a number of transmitter systems (including cholinergic and glutamatergic), has neuroprotective and anticonvulsant properties, and improves neuroplasticity. At the vascular level, it is found that this reduces the adhesion of erythrocytes to the vascular endothelium, prevents vasospasm and facilitates microcirculation. This diverse range of physiological effects is consistent with its use in a number of clinical indications [13, 14]. Piracetam and levetiracetam, the S-enantiomer, are derivatives of pyrrolidone that have similar chemical structures but have a clear pharmacological profile and therefore different clinical methods of application. A brain-specific stereoselective binding site to which levetiracetam and other S-enantiomers have a high affinity has been identified. In preclinical studies, piracetam significantly improves learning and memory; in contrast, levetiracetam has a lesser effect, but is much more active in preventing seizures [15]. Aniracetam from the group of racetams activates AMPA receptors and accelerates the synaptic transmission of neural messages in the central nervous system. AMPA is a subset of glutamate receptors that are important for neural communication, memory formation, and attention. Aniracetam enhances the secretion of norepinephrine, dopamine and serotonin, activates acetylcholine receptors and has a neuroprotective effect [16].

The pyrrolidone (2-oxopyrrolidine) family of chemicals has been the subject of research for more than three decades. Experimental and clinical work initially focused on their so-called nootropic effects; later there was information about the possibility of using their neuroprotection after stroke and use as antiepileptic drugs [17].

Given the structural similarity with known nootropics, further studies of new derivatives of 1-benzyl-4-pyrrolidin-2-one as a prototype of innovative

drugs with nootropic action is a very justified approach to targeted research. In our opinion, in order to achieve biosynergism, it is expedient to chemically modify 1-benzyl-4-pyrrolidin-2-one by combining in one molecule with another "structural matrix", namely the 1,2,4-triazole ring. Derivatives of 1,2,4-triazole are low-toxic, fairly easy to synthesize and highly reactive substances, which allows them to be easily combined in one structure with other pharmacophore fragments [18]. Scientists in European countries refer to the 1,2,4-triazole heterocyclic system as a privileged scaffold, as most of the synthesized derivatives of this heterocycle show some pharmacological activity and are related to different biotargets, which is considered an advantage in the implementation of the concept of multi-target drugs (concepts of multipurpose drugs) [19-20]. Our analysis of the scientific literature showed that despite the large number of publications on the functional derivatives of 1,2,4-triazole and pyrrolidine, the topic of combining them in one molecule in the context of "hybrid pharmacophore approach" remains virtually unexplored in the literature.

The therapeutic effect in the absence of the currently established general molecular mechanism of action makes it important to identify common to all nootropic drugs receptors and synaptic processes by which they have a modulating effect on cognitive functions and implement non-specific effects, namely: tranquilizing, sedative, hypnotic and psychogenic. Identification of these patterns will contribute to the optimization of pharmacotherapy of existing drugs and the development of new highly effective nootropic agents. It is known that the group of racetams has no affinity for tryptamine, dopamine, adenosine, opiate, benzodiazepine receptors, but is able to affect glutamate and acetylcholine receptors. Therefore, our planned docking studies will target these nootropic targets (glutamate receptor (N-methyl-D-aspartate (NMDAR)) (PDB ID: 5UOW), acetylcholine muscarinic and nicotinic receptors (PDB ID: 6PV7, 5CXV)).

N-methyl-D-aspartate (NMDAR) receptors are heterotetrameric ion channels that are assembled as diheteromeric or triheteromeric complexes. The GluN1 / GluN2A / GluN2B triheteromeric receptor was selected for docking in the presence of a GluN2B-specific allosteric modulator Ro 25-6981 (Ro), which was determined by cryogenic electron microscopy (cryo-EM) (PDB ID: 5UOW) [21, 22].

Nicotinic acetylcholine receptors are pentameric ion channels that mediate rapid chemical neurotransmission. The subtype of nicotinic $\alpha 3\beta 4$ receptors forms the main relay between the central and peripheral nervous systems in the autonomic ganglia. The nicotinic $\alpha 3\beta 4$ receptor in lipid and detergent media was selected for docking studies. Receptor structures in complex with nicotine, as well as $\alpha 3\beta 4$ -selective ligand AT-1001, supplemented by molecular dynamics can predict the selectivity of agonists [23].

Muscarinic acetylcholine receptors M1-M5 are associated with G-proteins and regulate many vital functions of the central and peripheral nervous system. In particular, the M1 and M4 receptor subtypes have become targets for new drugs for the treatment of neurological disorders such as Alzheimer's disease and schizo-

phrenia. For the study, we selected the crystal structures of muscarinic receptors M1 and M4, which are associated with the inverse agonist - tiotropium [24].

The aim of the study – to optimize the purposeful search for new compounds of nootropic action.

2. Planning (methodology) of research

1. At the first stage of purposeful search of new nootropic substances in order to theoretically substantiate the choice of the basic structure of 1-benzyl-4-pyrrolidin-2-one, empirical experience, logical-structural analysis and “hybrid-pharmacophore approach” were used.

2. The creation of a virtual database of potential nootropic agents was performed by structural modification of 1-benzyl-4-pyrrolidin-2-one by a combination through position C4 with a substituted 1,2,4-triazole system using the program Marvin Sketch 20.5.

3. The group of racetams is able to affect glutamate at acetylcholine receptors. Therefore, molecular docking was targeted at these targets (glutamate receptor (N-methyl-D-aspartate (NMDAR)) (PDB ID: 5UOW), acetylcholine muscarinic and nicotinic receptors (PDB ID: 6PV7, 5CXV)).

4. The choice of crystallographic models is due to the fact that they contained the corresponding ligands. This makes it possible to predict the affinity of the studied molecules to these targets.

5. Using molecular docking, Scoring functions were calculated, which indicate the enthalpy contribution to the value of free binding energy (Affinity DG) for the best conformational positions of the tested compounds and a detailed analysis of the geometric location of the leading compounds in the active sites of these receptors.

3. Materials and methods of research

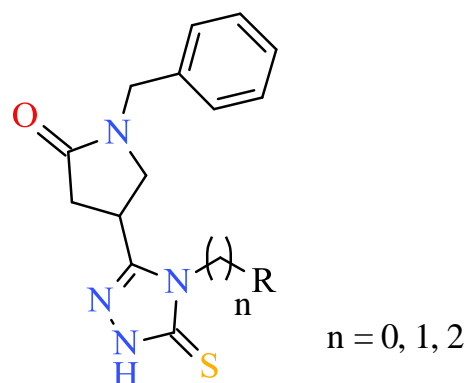
The generation of the database for virtual screening was performed using the program Marvin Sketch 20.5.

Autodock 4.2 software package was used for receptor-oriented flexible docking. Preparation of ligands was performed using the program MGL Tools 1.5.6. Optimization of ligands was performed using the program Avogadro. For calculations in Autodock 4.2, the original data formats of the receptor and ligands were converted to a special PDBQT format. Active centers of macromolecules from Protein Data Bank (PDB) of neurotropic receptors (PDB ID: 5UOW, 5CXV, 6PV7) were used as biological targets for docking. Receptor maps were prepared in MGL Tools and AutoGrid. Water molecules, ions and ligand were removed from the PDB file ID. The following docking parameters were set: the translational step was 2 Å, the torsional freedom coefficient was 0.2983. The cluster tolerance is 2 Å. External lattice energy – 1000, maximum initial energy – 0, maximum number of attempts – 10 000. Number of structures in the population – 150, maximum number of stages of energy estimation – 2500000, maximum number of generations – 27 000, number of structures that pass to the next generation – 1, the level of gene mutation – 0.02, the level of the crossover – 0.8, the method of the crossover - arithmetic. The α -Gaussian distribution parameter is equal to 0, the β -parameter of Gaussian distribution is 1. Visual analysis of complexes

of substances in the active center of receptors (PDB ID: 5UOW, 5CXV, 6PV7) was performed using Discovery Studio Visualizer.

4. Research results

The object of the study was selected promising nootropic molecules from the group of racetams - new derivatives of 1-benzyl-4-pyrrolidin-2-one. At the first stage of a purposeful search for new nootropic BAS by structural modification of the basic structure of 1-benzyl-4-pyrrolidin-2-one by combination through position C4 with a substituted 1,2,4-triazole system using the program Marvin Sketch 20.5. Was generated a virtual database of new compounds in the amount of approximately 70 thousand molecules of general formula:



The introduction of a fragment of 1,2,4-triazole-5-thione (a potential electron pair donor) into the basic structure of 1-benzyl-4-pyrrolidin-2-one should promote the formation of hydrogen bonds with the hydrogen atoms of the biotarget with a sufficient partial charge. Functionalization of the basic structure of 1-benzyl-4-(4-R-5-sulfonylidene-4,5-dihydro-1H-1,2,4-triazol-3-yl)pyrrolidin-2-one is provided by additional introduction in position C1 and C4 1,2,4-triazole ring aromatic and heterocyclic moieties that may increase activity. The introduction of alkyl chains of different lengths between the 1,2,4-triazole ring and the corresponding substituents should ensure optimal lipophilicity of the molecules, which is an important factor in the search for BAS, which must pass through the GEB.

According to the results of 3D-pharmacophore screening and molecular docking to nootropic targets of compounds of the virtual base, a promising group of compounds was identified – derivatives of 1-benzyl-4-(4-R-5-sulfanylidene-4,5-dihydro-1H-1,2,4-triazol-3-yl)pyrrolidin-2-one, which have affinity for nootropic targets. In the tab. 1 scoring functions are given, which indicate the enthalpy contribution to the value of free binding energy (Affinity DG) for the best conformational positions of all compounds of the selected perspective group.

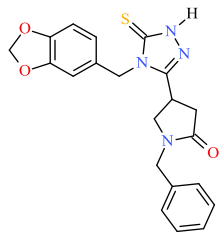
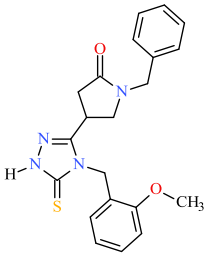
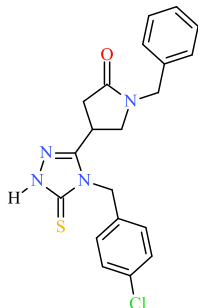
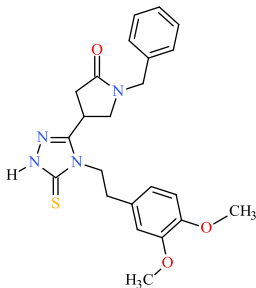
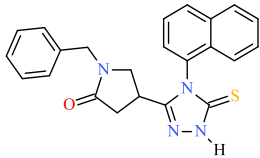
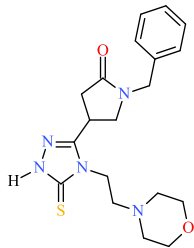
An analysis of the geometric location in the active sites of nootropic receptors of “hit compounds” 2 and 11 (Fig. 1), which allowed to formulate some hypotheses about possible ways of interaction of compounds of the generated base with biotargets.

Table 1

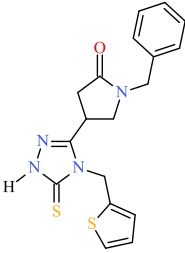
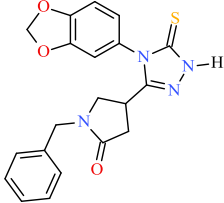
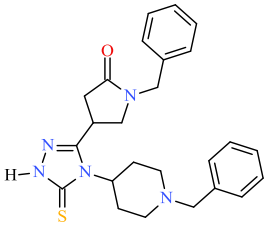
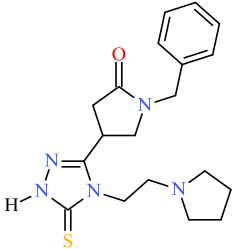
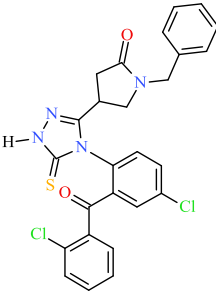
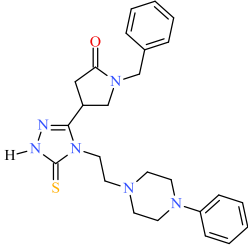
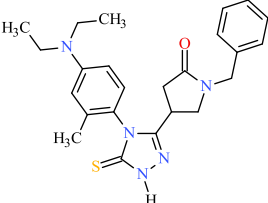
The value of Afinity DG for the best conformational positions of 1-benzyl-4- (4-R-5-sulfonylidene-4,5-dihydro-1H-1,2,4-triazol-3-yl) pyrrolidin-2-one in the complex with neurotropic targets (PDB ID: 5UOW, 5CXV, 6PV7)

No.	Structure	Afinity DG, kcal/mol		
		5UOW	5CXV	6PV7
1	2	3	4	5
1		-6.2	-7.1	-6.0
2		-9.0	-9.3	-7.2
3		-7.2	-7.6	-6.6
4		-6.7	-8.2	-6.6
5		-8.4	-8.7	-7.0
6		-6.4	-8.1	-6.0

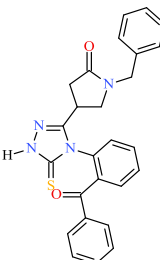
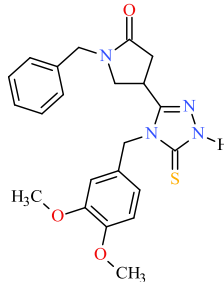
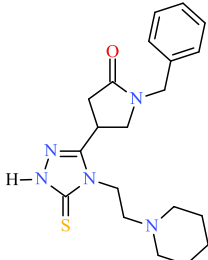
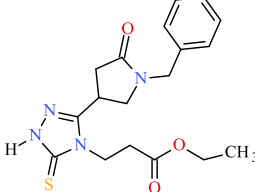
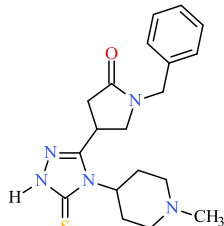
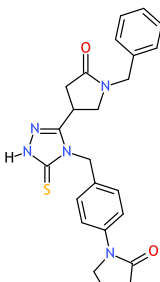
Continuation of Table 1

1	2	3	4	5
7		-7.1	-8.5	-6.5
8		-7.4	-8.5	-6.2
9		-7.4	-8.8	-6.6
10		-6.5	-7.8	-5.8
11		-9.2	-9.9	-7.5
12		-6.5	-7.8	-6.2

Continuation of Table 1

1	2	3	4	5
13		-7.8	-8.0	-6.7
14		-7.7	-9.4	-6.6
15		-7.9	-8.9	-6.7
16		-7.3	-8.2	-6.1
17		-8.6	-9.9	-7.5
18		-7.5	-8.7	-7.1
19		-8.0	-8.7	-5.9

Continuation of Table 1

1	2	3	4	5
20		-8.9	-9.2	-7.1
21		-7.8	-8.6	-5.8
22		-7.3	-8.1	-6.2
23		-6.5	-7.6	-5.6
24		-6.4	-7.7	-6.4
25		-7.9	-8.9	-6.9

Continuation of Table 1

1	2	3	4	5
26		-7.8	-7.7	-6.4
27		-7.7	-9.2	-7.0
28		-7.8	-7.8	-7.2
29		-8.0	-8.8	-7.4
30		-7.5	-9.2	-6.1
31		-7.2	-8.1	-6.3

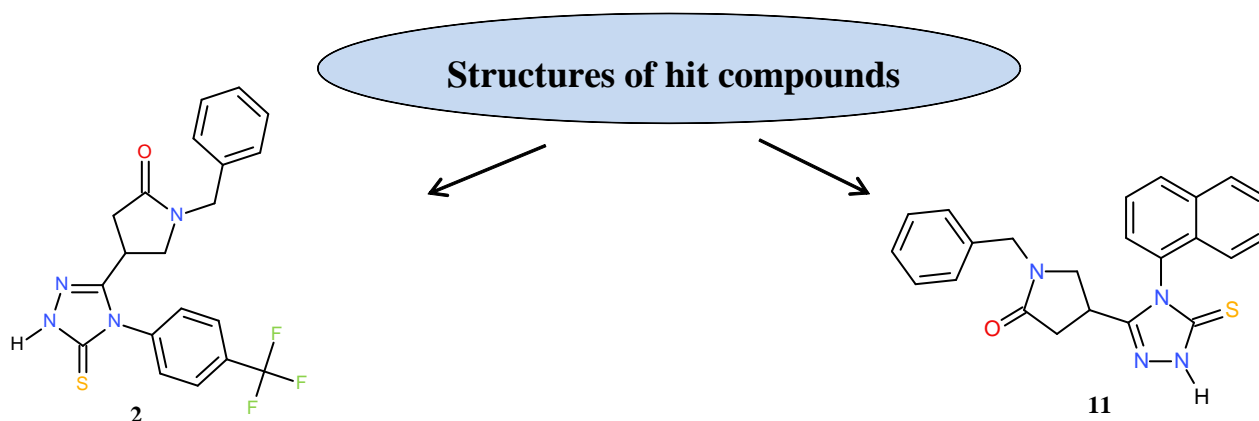
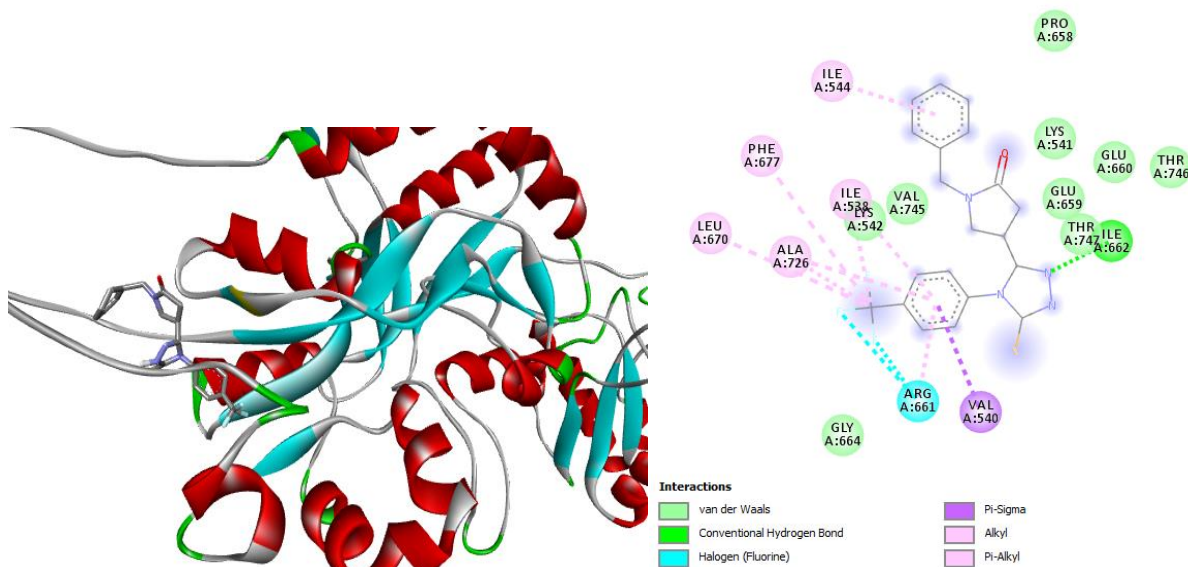


Fig. 1. Structures of hit compounds

A detailed analysis of the geometric arrangement of molecule **2** at the active site of the N-methyl-d-aspartate receptor (NMDAR) (PDB ID: 5UOW) showed that the bonds between the fluorine atoms of the trifluoromethyl substituent and the amino acid donor Argin1 ARG are involved in the formation of the complex. The presence of hydrogen bonds between the Nitrogen atom of the 1,2,4-triazole ring and the ILE662 isoleucine residue also contributes to the stabilization of the formed complex.

The formation and stabilization of the complex is facilitated by the π - σ bond that occurs between the aryl moiety and the residue of valine VAL540. Additionally stabilize the complex of π -Alk and Alk interactions between aromatic fragments of the molecule and trifluoromethyl substituent with amino acid residues ILE544, ILE538, PHE677, LEU670, ALA726, ARG661 (Fig. 2).

Fig. 2. Superposition of molecule **2** and diagram of intermolecular interactions in complex with N-methyl-d-aspartate receptor (NMDAR) (PDB ID: 5UOW)

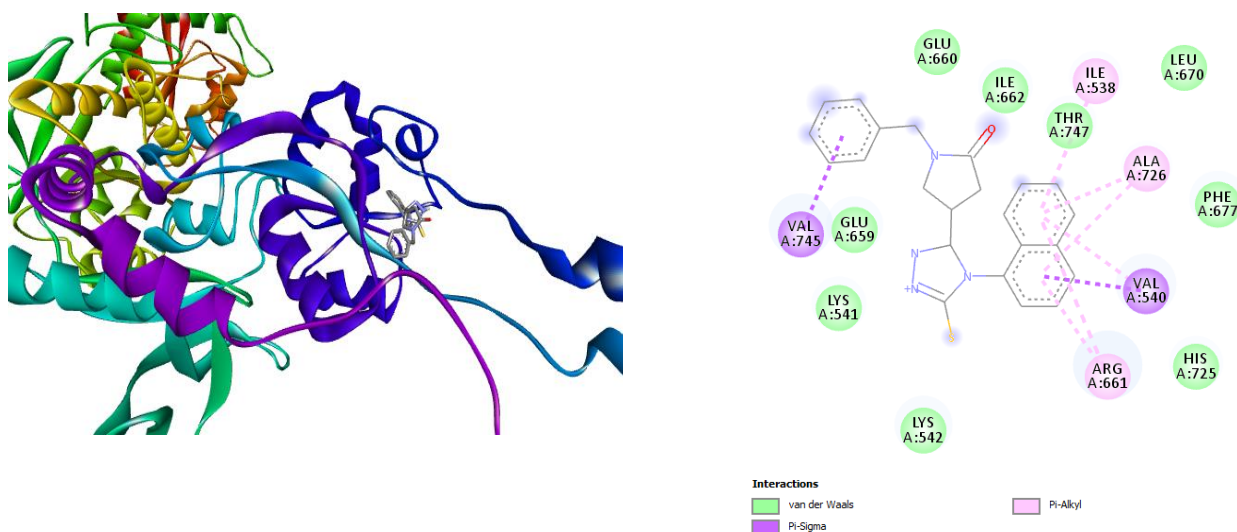


Fig. 3. Superposition of molecule **11** and diagram of intermolecular interactions in complex with N-methyl-d-aspartate receptor (NMDAR) (PDB ID: 5UOW)

Compound **11** forms a complex with the N-methyl-d-aspartate receptor due to the π - σ bond between the phenyl moiety and VAL745 residues. Π - σ binding also occurs between the naphthyl moiety and the VAL540 residue. Stabilization of the π -Alk complex occurs due to the interaction between the naphthyl fragment and amino acid residues ILE538, ALA726, VAL540, ARG661 (Fig. 3).

The complex between molecule **2** and the muscarinic acetylcholine receptor (PDB ID: 5CXV) is formed due to the halogen bonds between the fluorine atoms of the trifluoromethyl substituent and the residues GLU401, TYR85, LEU86, the hydrogen bond between the oxygen atom of pyrrolidine-2-one and the residue of TYR381. π -H The interaction occurs between the sulfur atom of the thionic group and the amino acid residue TYR404. π -Anionic and π - σ interactions are formed between the phenyl fragments of the molecule and the GLU401 and TYR179 residues. A carbon-hydrogen bond is also present between the Fluorine atom and the glycine GLY89 residue. Additional stabilization of the complex is facilitated by π - π , π -Alk and Alk interactions that occur between the leucine LEU88 residue and the phenyl ring of the studied molecule (Fig. 4).

The formation of a complex of molecule **11** with acetylcholine receptor (PDB ID: 5CXV) involves a hy-

drogen bond (occurs between the nitrogen atom of 1,2,4-triazole ring and the tyrosine residue TYR381) and the π -anionic interaction between the phenyl ring and the glutamine acid GLU401.

Intermolecular π - π interactions occur between phenyl and naphthyl substituents with amino acid residues TYR85 and TYR400. Acceptor-acceptor binding is also observed between the Oxygen atom of pyrrolidin-2-one and the TYR82 tyrosine residue. Additionally, the π -Alk complex of interaction between the phenyl fragment of the molecule and the leucine residue LEU86 is stabilized (Fig. 5).

The complex of molecule **2** with the nicotinic acetylcholine receptor (PDB ID: 6PV7) occurs due to the hydrogen bond between the Hydrogen of the 1,3,4-triazole ring and the ILE85 residue. Also, a hydrogen bond is formed between the distal nitrogen atom of the 1,2,4-triazole ring with the LYS87 residue. Halogen bonds are formed between the fluorine atom of trifluoromethyl and the amino acid residues of valine and asparagine (VAL102, ASP104). Hydrogen and carbon-hydrogen bonds between the fluorine atom, the alkyl radical and the residues GLN101, LYS81, TYR151 also stabilize the formed complex. π -Cationic and π -anionic interactions occur between the phenyl rings of the molecule and the residues LYS87, ASP89 (Fig. 6).

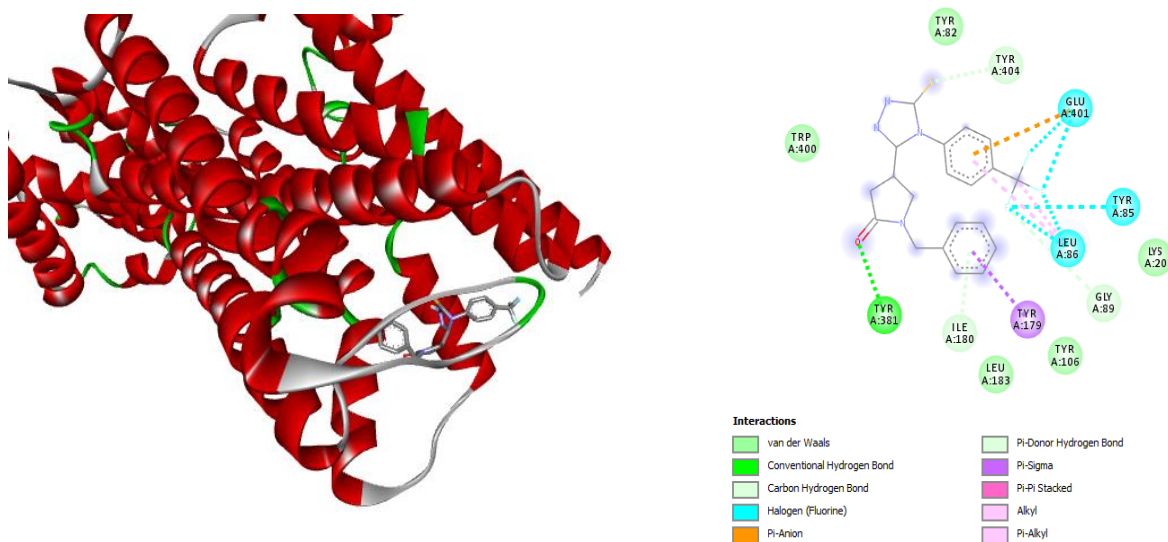


Fig. 4. Superposition of molecule 2 and diagram of intermolecular interactions in complex with muscarinic acetylcholine receptor (PDB ID: 5CXV)

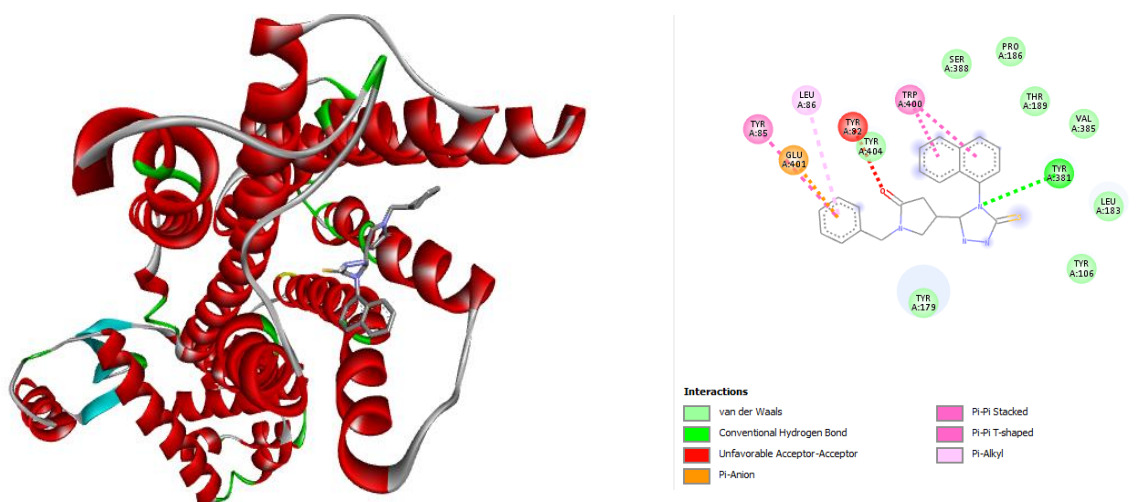


Fig. 5. Superposition of molecule 11 and diagram of intermolecular interactions in complex with muscarinic acetylcholine receptor (PDB ID: 5CXV)

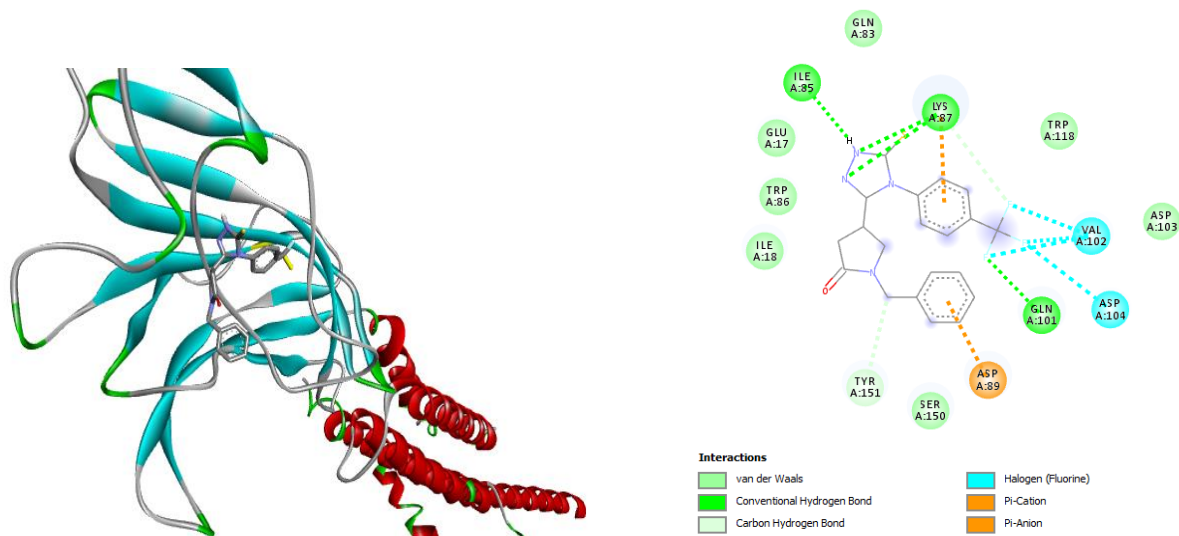


Fig 6. Superposition of molecule 2 and diagram of intermolecular interactions in complex with nicotinic acetylcholine receptor (PDB ID: 6PV7)

Two π - σ bonds between phenyl and naphthyl rings for leucine residues are involved in the formation of the complex of compound 11 with the nicotinic acetylcholine receptor (LEU468, LEU222). The π -sulfur interaction occurs between the sulfur atom of

the thionic group and the PHE137 phenylalanine residue. Stabilization of the complex is facilitated by π -Alk interactions between aromatic fragments of the molecule and residues LEU468, LEU223, LEU465, ILE219 (Fig. 7).

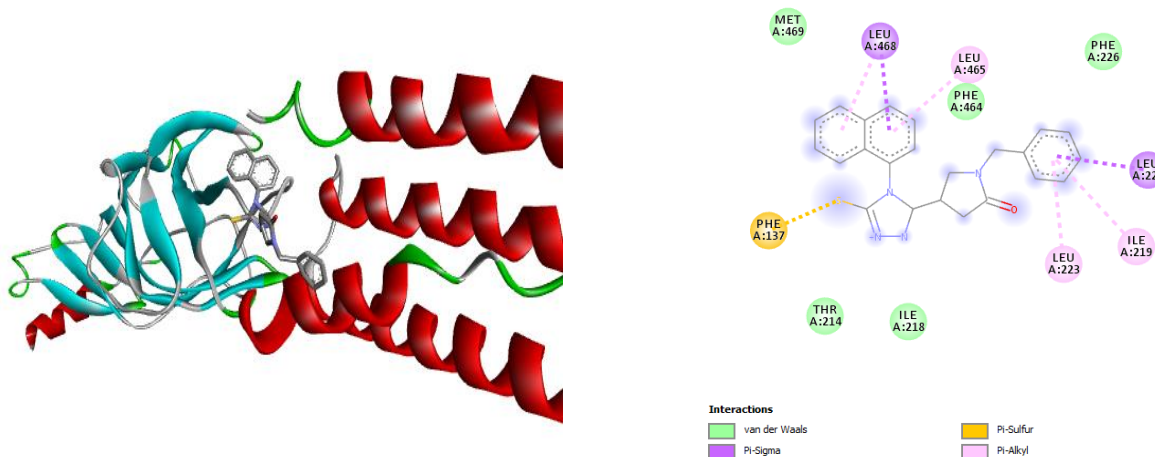


Fig 7. Superposition of molecule 11 and diagram of intermolecular interactions in complex with nicotinic acetylcholine receptor (PDB ID: 6PV7)

5. Discussion of research results

Piracetam and aniracetam are known pyrrolidine allosteric modulators [25, 26]. Previous research has already determined the structure of the ligand binding domain of glutamate receptor subtypes with piracetam and aniracetam. Both drugs bind in a very similar way, which indicates a slight specificity of the subunit. However, the binding sites of piracetam and aniracetam are significantly different. Aniracetam binds to a symmetrical region in the center of the dimeric interface. Piracetam binds to several sites along a low-occupancy dimeric interface, one of which is a unique binding site for potential allosteric modulators. This new site may be important in the development of new allosteric regulators [27].

The ability of racetams to act on glutamate receptors leads to the activation of acetylcholine receptors. There is currently no data on their direct linking. Therefore, the search for new nootropic molecules of this series that would have an affinity for these biotargets is an important area of docking research.

The activity of promising molecules relative to the studied receptors (PDB ID: 5UOW, 5CXV, 6PV7) is realized by the formation of complexes between them, the stability of which is ensured mainly by the energetically favourable geometric arrangement of ligands in the active center of these acceptors and the formation of hydrogen bonds between them, intermolecular electrostatic and donor-acceptor interactions. As a result, the thermodynamic probability of such binding is confirmed by the negative values of the scoring functions (Afinity DG, kcal / mol) (Table 1).

Given the detailed analysis of the geometric location of "hit compounds" in the active sites of nootropic targets, the formation between them of a number of intermolecular interactions, calculated values of scoring functions, we can assume that the manifestation of affinity for selected targets contribute:

- the emergence of strong intermolecular hydrogen bonds between the compounds of the virtual base and the amino acid residues of the targets,

- stabilization of the formed "target molecule" complex by intermolecular interactions with charge transfer (π - σ , π - Sulfur, π - anion, carbon-hydrogen bond, π - π , Alk and π - Alk).

The formation and stabilization of complexes are provided by the modification of basic molecules with sulfonyl, the presence in their structure of alkyl-, oxy-, halogen-substituted nitrogen-containing cyclic moieties and aromatic nuclei. Mandatory for the manifestation of activity is the presence in the structure of the methylene group between cycles, which provides flexibility of the molecule and allows it to occupy the most energetically advantageous conformational position in the active center of the biotarget.

Study limitations. The possibility of using *in silico* studies does not remove the relevance of *in vivo* studies, but has such advantages as cost-effectiveness, high reproducibility, no need for chemical synthesis of a huge number of compounds.

Prospects for further researches. According to the results of the research, a group of 1-benzyl-4-(4-R-5-sulfonylidene-4,5-dihydro-1H-1,2,4-triazol-3-yl) pyrrolidin-2-one derivatives was found to have affinity for nootropic biotargets and promising for further synthetic studies.

6. Conclusions

An order to search for new molecules of nootropic action, a virtual base of 1-benzyl-4-pyrrolidin-2-one derivatives was generated and analyzed.

According to the results of docking studies, a group of derivatives of 1-benzyl-4-(4-R-5-sulfonylidene-4,5-dihydro-1H-1,2,4-tri-azol-3-yl) pyrrolidin-2-one was detected; they have an affinity for nootropic biotargets and promising for further synthetic studies.

Structural fragments of new compounds have been identified, the presence of which increases the affinity for nootropic biotargets.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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